Author/s:
Chen, J;Easwaralingam, N;Warrier, S;Ong, A;Carson, EK;Mak, C;Snook, K;Middleton, K;Parker, A;Palmieri, C;Spillane, A;Mann, GB;Lim, E;Segara, D

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Chen Julia (Orcid ID: 0000-0003-1278-7763)
Easwaralingam Neshanth (Orcid ID: 0000-0002-2616-3751)

Window of Opportunity Treatment in Breast Cancer

Julia Chen Bsc(Med)Hons, MBBS[1,*], Neshanth Easwaralingam MBBS(Hons), FRACS[1,*], Sanjay Warrier MBBS, FRACS[2,3], Andrew Ong MBChB, FRACS[4], Emma-Kate Carson MBChB, FRACP[1,4], Cindy Mak MBBS, FRACS[2], Kylie Snook BMED(Hons), FRACS[5] , Kate Middleton BMedSc, MBBS[1], Andrew Parker MBBS(Hons), FRCPA[1], Carlo Palmieri MRCP, PhD[6], Andrew Spillane MD, FRACS[5,7,8], G Bruce Mann FRACS, PhD[9,10], Elgene Lim FRACP, PhD[1,*], Davendra Segara FRACS, PhD[1,*]

1. Garvan Institute of Medical Research and St Vincent's Hospital, University of New South Wales, Sydney, Australia
2. Chris O'Brien Lifehouse and University of Sydney, Australia
3. Royal Prince Alfred Hospital Institute of Academic Surgery, University of Sydney, Australia
4. Campbelltown Hospital and University of Western Sydney, Australia
5. Breast and Surgical Oncology at The Poche Centre and Northern Clinical School, University of Sydney, Australia
6. University of Liverpool, Clatterbridge Cancer Centre, NHS Foundation Trust, and Royal Liverpool University Hospital, Liverpool, United Kingdom
7. Mater Hospital, North Sydney, Australia
8. Royal North Shore Hospital, St Leonards, Sydney, Australia
9. Royal Melbourne and Royal Women's Hospital, Melbourne, Australia
10. Department of Surgery, The University of Melbourne, Melbourne, Australia

* These authors contributed equally.

Corresponding authors:

Elgene Lim
e.lim@garvan.org.au
Garvan Institute of Medical Research, 370 Victoria St, Darlinghurst NSW 2010

Davendra Segara
d.segara@garvan.org.au
St Vincent's Clinic, Suite 706, 438 Victoria St, Darlinghurst NSW 2010

Abstract

Window of opportunity therapies, which involve short term administration of systemic therapy between cancer diagnosis and surgery, have raised significant interest in recent years as a mean of assessing the sensitivity of a patient's cancer to therapy prior to surgery. There is now compelling evidence that in patients with early stage hormone-receptor positive (HR+) breast cancer, a 2 week preoperative treatment with standard hormone therapies in a preoperative window period provides important prognostic information, which in turn helps to aid decision making regarding treatment options. Changes in short-term biomarker endpoints such as cell proliferation measured by Ki-67 can act as surrogate markers of long-term outcomes. Paired tissues obtained pre- and post-investigational treatment, without having to subject the patient to additional biopsies, can then be used to conduct translational research to investigate predictive biomarkers and pharmacodynamics. In this

review, we will examine the utility and challenges of WOTs in breast cancer in the current literature, and the current Australian and international trial landscape in this clinical space.

Main text (2757 words)

Introduction

Window of Opportunities Therapies (WOTs) involve a short period of preoperative systemic therapy between diagnosis and primary surgery. While this approach is not uncommon in the clinical setting, particularly for ensuring there is no progression when there are delays to primary surgery, it is increasingly being employed in a more standardised fashion in a broader population, with a functional readout of biomarkers indicative of treatment response. Unlike standard preoperative systemic therapy approaches, the goal of WOT is to identify a change in a specific biomarker rather than to downstage the cancer. It easily fits into the window patients often have to wait for primary breast surgery, therefore having little or no impact on the time to surgery. This approach is most validated in the setting of early stage HR+ breast cancer using Ki-67 as a biomarker, following 2 weeks of preoperative endocrine therapy (ET).

WOT is also frequently utilised in clinical trials setting as a relatively cost and time-efficient tool to functionally assess the response of cancer to new therapies. It provides an opportunity for the rapid assessment of new compounds to provide initial pharmacodynamic parameters (1). The availability of pre- and post-treatment tissue allows the exploration of biological mechanisms of the drug's activity. In most instances, the definitive treatment is surgery, meaning a substantial amount of post-treatment tissue is available for extensive testing for mechanisms of drug response, drug resistance and predictive biomarkers. This overcomes one of the major barriers of new cancer therapy development, where pre-clinical models are limited by the scarcity of *in vivo* and *in vitro* models that accurately mimic tumour biology in humans (2) In this review, we will examine the utility and challenges of WOTs in breast cancer, and clinical trials in this setting.

Systemic therapy in hormone-receptor positive breast cancer.

ET remains the bedrock of systemic adjuvant therapy in HR+ breast cancers. However, there is a large degree of heterogeneity of biological behaviour within these cancers and their response to ET (3). Luminal breast cancers are typically characterised by a long natural history and an ongoing risk of recurrence even after completion of systemic adjuvant therapy (4). Therefore 5 years of adjuvant ET is not optimal for all patients with HR+ breast cancer. A major adjunct to adjuvant ET has been the addition of chemotherapy in patients with higher risk of recurrence (5). Another approach to these patients is by intensifying adjuvant ET, either through extended adjuvant ET duration, or by combining ovarian suppression with ET in premenopausal women (6-8). These approaches however come at a cost of increased morbidity from toxicities of treatment and long-term consequences such as osteoporosis and cardiovascular disease. The key to these approaches is to identify the subset of patients who may benefit most as the absolute benefits are small overall and negligible in patients with low risk disease.

Window of opportunity endocrine therapy in breast cancer

A major difference between WOTs and above approaches is that WOTs functionally assess a tumour's response to therapy, while the other approaches are solely based on tumour characteristics, independent of response to therapy. A summary of WOT trials of ET in breast cancer is listed in **table 1a**.

Tamoxifen was the first endocrine agent to be evaluated in a WOT trial which randomised 103 breast cancer patients to tamoxifen or placebo in the preoperative window period with a median treatment duration of 3 weeks. A significant decrease in Ki-67 was seen in the tamoxifen-treated patients but not in the placebo group (9). Post-WOT Ki-67 predicted both recurrence-free and overall survival (10). In other studies, different doses and formulations of tamoxifen were evaluated, demonstrating similar effects on Ki-67 expression (11, 12). The expression of other breast cancer-related biomarkers including insulin-like growth factor-1 and sex hormone binding globulin demonstrated a linear dose-response relationship with tamoxifen in this study.

Aromatase inhibitors (AIs) are the most extensively studied ET in the window setting. The IMPACT trial randomised 330 patients to receive neoadjuvant tamoxifen, anastrozole or a combination of the two for 12 weeks. This trial was designed to match the ATAC trial, which compared same treatment arms in the adjuvant setting and showed improvement in recurrence-free survival in the anastrozole arm (13). Although IMPACT was not strictly a WOT study, biopsies were taken at 2 weeks post-treatment and biological changes in proliferation were assessed by Ki-67 staining, yielding data at a time point consistent with most WOT studies (14). A reduction in Ki-67 was significantly more pronounced in the anastrozole group compared to the tamoxifen group (76% vs 59.5%), mirroring results of the ATAC trial. Further analyses suggested that higher Ki-67 expression after 2 weeks of therapy was associated with worse recurrence-free survival (15).

Subsequent WOT studies with AIs have explored genome-wide expression profile in attempts to understand the underlying tumour biology and effects of these drugs on a molecular level. In one study, whole exome sequencing of tumours following 10-21 days of WOT with an AI revealed a correlation between genomic aberrations such as *FGFR1* and *CCND1* amplification, and poor response to AI as indicated by high Ki-67 post-treatment (16). RNA sequencing revealed the presence of intrachromosomal *ESR1* fusion transcripts and increased expression of gene signatures indicative of enhanced E2F-mediated transcription and cell cycle processes in cancers with high Ki-67 (16). Another study observed a similar increased proportion of *FGFR1* amplification in tumours that did not have a Ki-67 response following WOT with letrozole compared with responding tumours. The translational relevance of this finding is supported by preclinical studies that showed FGFR antagonists as effective therapy in endocrine-resistant, *FGFR1*-amplified models (17). These data suggest that WOT followed by genomic profiling not only provides insights into mechanisms of intrinsic endocrine resistance, it may also be used to identify potentially targetable alterations to overcome this resistance.

The largest WOT study in breast cancer to date is the phase 3 POETIC trial (18). A total of 4,486 postmenopausal women with early-stage HR+ breast cancer were randomised in 2:1 ratio to receive an AI or placebo for 2 weeks prior to and after surgery. Patients then received standard adjuvant therapy. Preliminary analysis after a median follow-up of 60.7 months found that 9.1% of patients had a recurrence of their breast

cancer. There was no evidence of an improved time-to-recurrence in the treatment group compared to control group (8.8% vs. 9.6%). However, Ki-67 at baseline and at 2 weeks following WOT provided significant and independent prognostic information. Patients with a low Ki-67 (<10%) had a good prognosis and had little additional prognostic data to gain from WOT AI. In contrast, patients whose baseline Ki-67 was high (≥10%) could be stratified into risk groups based on their response to 2 weeks of WOT. The 5-year absolute risk of recurrence was significantly higher in patients with a Ki-67 ≥10% before and after treatment compared with those whose Ki-67 had reduced from ≥10% to <10% following WOT (19.6% vs 8.9%) (18). The hazard ratio for patients with high Ki-67 at both time points was 2.22 (p <0.001). This study supports the routine use of WOT outside clinical trials as a prognostication tool. There are however no current guidelines to use Ki-67 response information to guide subsequent adjuvant therapy.

There are a number of ongoing trials evaluating various endocrine-based therapies in HR+ breast cancer (**Table 1b**). The WinPro study is one such investigator-initiated study funded by Cancer Council of NSW and Centre for Translational Breast Cancer Research currently recruiting across Australia. This study evaluates 2 weeks of ET alone or in combination with prometrium (microionised progesterone) in postmenopausal patients with newly diagnosed early-stage ER/PR-positive, HER2-negative breast cancer (ClinicalTrials.gov identifier NCT03906669). The rationale for this study is based on seminal preclinical research that has shown additive anti-tumour effect of progesterone in combination with ET in explant and xenograft models (19). A total of 200 patients will be recruited, randomised to receive letrozole, letrozole plus prometrium or tamoxifen plus prometrium between diagnosis and definitive surgery. The primary endpoint is to determine geometric mean suppression of centrally assessed Ki-67 after two weeks of intervention, compared with baseline. Translational endpoints including evaluating a gene set as a predictive biomarker for a reduction in Ki-67 and changes in markers such as Bcl-2, caspase 3, hormone receptors and mRNA expression in tumours following intervention. Functional profiling of endocrine-resistant tumours will hopefully provide more insights into pathways of primary endocrine resistance and potential new therapeutic targets to overcome these. Two similar WOT trials (PIONEER trial, ClinicalTrials.gov identifier NCT03306472; PEARL trial, ISRCTN23662758) are running in parallel in United Kingdom with a plan for combined analysis at the completion of these three trials. Another WOT trial currently accruing in Australia is GDC-9545 (an oral oestrogen receptor degrader, ClinicalTrials.gov identifier NCT03916744), which aims to evaluate the pharmacodynamics and pharmacokinetics at three different doses in parallel with a phase 1 study conducted in the advanced/metastatic setting.

WOT trials in breast cancer with non-endocrine therapy

In addition to ET, a number of non-endocrine therapies have been tested in the WOT setting, typically but not always in combination with an ET backbone, and with standard ET as a control arm. CDK4/6 inhibitors such as ribociclib and palbociclib have been evaluated in combination with AI in WOT setting to assess anti-proliferative response as well as pharmacokinetics, genetic profiling and safety (20, 21). Results showed significant reduction in Ki-67 expression with absence of drug-drug interaction between these drugs and AI. Further studies have now established the use these combinations as standard first line treatments for metastatic HR+ breast cancers (22, 23). The antiproliferative effects of metformin have been studied in multiple WOT trials and demonstrated a trend

toward a decrease in Ki-67 and apoptosis (24-26). Statins were also assessed in the WOT setting and was found to reduce proliferation only in tumours that express HMG-CoA reductase, via inhibition of MAPK pathway (27). While these results have not yet translated into clinically meaningful treatments, they provide valuable insights into their mechanisms of action *in vivo*.

Molecular targeted therapies tested in the WOT setting include epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) gefitinib and erlotinib, vascular endothelial growth factor antibody bevacizumab and EGFR/HER2 TKI lapatinib. These trials did not only assess antiproliferative effects of these drugs against ET as standard treatment, but also incorporate exploratory endpoints such as drug-induced molecular changes (28) and interaction between different gene signatures (29), which enables identification of potential predictive biomarkers. These studies demonstrate the feasibility of WOTs with targeted agents to guide development of new therapeutic options.

Tissue and Short-term Biomarker analysis in WOT

Ki-67 is the most commonly used biomarker in endocrine-based WOT in breast cancer. A change in Ki-67 is a validated endpoint linked to treatment efficacy and prognosis (15, 30). Major limitations of Ki-67 however include variability due to tumour heterogeneity, duration of tissue ischaemia, duration of fixation, immunohistochemical technique used and inter-observer variation (31). To overcome some of these limitations, the International Ki-67 in Breast Cancer Working Group has published recommended guidelines for the assessment, interpretation and scoring of Ki-67 (32). Adherence to such standardised protocols would help to improve between-laboratory and between-study comparability of this biomarker. In clinical trials setting, central processing of specimens in the same laboratory using standardised protocols and ideally scoring by the same pathologist would also help to mitigate some of these shortfalls.

Evidence for the utility of Ki-67 as a marker of treatment response in other cancers is less well validated, hence the optimal biomarker endpoint for WOTs outside of breast cancer context remains unknown. Other molecular endpoints, such as changes in cell cycle regulators or phosphorylation of targeted growth factors have been utilised both in breast cancer (28, 33) and other types of cancers (34, 35). These represent potentially feasible endpoints for future window studies but would require standardisation and validation to establish their routine use.

With increased utility of more complex techniques such as RNA-based analyses in molecular studies, there is also increased reliance on the quality of preserved tissue. Formalin-fixing and paraffin embedding is the standard form of preservation for biopsy specimens. However, nucleic acids extracted from formalin-fixed paraffin-embedded tissues are often fragmented and chemically modified, making it challenging for isolation of high-quality RNA for genetic profiling (36). Fresh frozen tissues are ideal in overcoming this challenge but require an additional pre-treatment research biopsy. However, for the measurement of immunohistochemistry-based biomarkers such as Ki-67, a dedicated research biopsy is not required, as it can be performed on the diagnostic core biopsy.

Optimal WOT Trial Design

The ideal trial design for a WOT should involve treatment with the investigational agent for a short period of time, with no delay in curative treatment. The acceptable interval between diagnosis and definitive treatment is not well-defined in the literature, but treatment within 4 weeks of diagnosis is usually considered acceptable (37). The treatment duration should also consider the pharmacokinetics of the drug, such that there is sufficient time to reach steady state. This poses a limitation for drugs with a prolonged half-life. Due to the time constraint of such studies, screening and consent should ideally be completed at the time of diagnosis. This allows investigators to combine standard investigations with those required by the trial, avoiding the need for repeat biopsies or imaging. The primary endpoint should ideally be a parameter that has been validated as a surrogate marker of treatment activity that affects survival outcomes (38). Another important aspect is evaluation of drug safety and toxicity. Given that these studies are generally conducted in patients prior to their curative surgery, the toxicity profile should be well-studied prior to initiation of treatment to minimise side effects with resultant delays in their definitive treatment. Drugs that may complicate surgery, such as by potentially affecting wound healing, blood cell counts or function are not ideal in this setting.

Study recruitment can be hindered by the need for an additional pre-treatment research biopsy and in some cases serial preoperative imaging, which may dis-incentivise patients. One study found that only 26.7% of patients with newly diagnosed operable breast cancer were agreeable to participate in WOT trials (39). Hence trials with limited additional investigation and biopsies which can be incorporated into a patient's routine work flow prior to surgery will likely have a higher participation rate. Finally, and most importantly, precise co-ordination and good communication within the multi-disciplinary team is mandatory. A lack of awareness from any member of the multi-disciplinary team can impact protocol compliance, timely processing of samples and administration of treatment.

Future directions

The current common practice for early HR+ breast cancers involves proceeding directly to surgery followed by adjuvant treatments, and in a minority of cases, having neoadjuvant systemic therapy to downstage the breast cancer. In Australia, it is not uncommon for there to be a 2 to 4-week window between diagnosis and surgery. With the emerging prognostic value of endocrine WOTs, this window represents an opportunity to incorporate endocrine-based WOT into standard practice for patients (**Figure 1**), especially those with a high baseline Ki-67. This is at a minimal cost to patients given well-known safety profile of tamoxifen and AIs, no need for additional investigations and does not impact on the timeliness of their surgical treatment. It will however, provide valuable information regarding the functional response of their tumours, which can then be used as an independent prognostic predictor when considering adjuvant treatment recommendations. Additionally, this strategy will enable the opportunity for biobanking valuable paired pre- and post-treatment tissue for translational research. A major clinical challenge that needs to be addressed is the best strategy to manage patients who do not obtain a Ki-67 treatment response to WOT, an area where there is little data. At present, one could consider performing a multi-gene assay to weigh up the addition of chemotherapy to ET, or extended ET.

In the context of drug development, there is an increasing number of WOT trials being conducted in Australia and internationally. These represent a cost-effective strategy to generate short-term functional data and biological information on molecular pathways altered by treatment, which will provide opportunities to discover relevant predictive biomarkers for patient selection in subsequent studies, significantly reducing the cost of trialing drugs in a larger, undefined patient population. The identification of altered molecular mechanisms may also be hypothesis-generating whereby evidence of response to treatment via a particular pathway may provide the rationale to test the same agent in a different disease modulated by a similar pathway. Future development may see the use of WOTs as a key modality in the new era of targeted therapies and emerging field of precision medicine using pan-omic analyses.

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